REMARKS

In response to the Office Action dated July 14, 2009, Applicants amended claims 45, 47, and 49. No new matter was added by these amendments. Reconsideration of the instant application is respectfully requested in view of the amendments above and the following remarks.

The instant invention is directed, *inter alia*, to methods of inducing bone formation, proteoglycan synthesis, or osteoblast differentiation in a mammal comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and an osteoinductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 protein. The osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP, or LMP-1s.

1. Claims 45, 47, and 49.

Claims 45, 47, and 49 were re-written in independent form. These claims are directed to methods of inducing bone formation, proteoglycan synthesis, or osteoblast differentiation in a mammal comprising administering an effective amount of a fusion polypeptide consisting a protein transduction domain and an amino acid sequence selected from the group consisting of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8 and combinations thereof.

Claims 45, 47, and 49 were rejected only based on 35 U.S.C § 112, second paragraph, as dependent on claims 7, 21, and 36 because it was allegedly unclear to what the term "LMP-1s" recited in claims 7, 21, and 36 was referring. Because these claims 45, 47, and 49 no longer depend on claims 7, 21, and 36, respectively, and do not include the term "LMP-1s" this rejection is moot. Accordingly, Applicants respectfully submit that these claims are in condition for allowance.

2. Rejection under 35 U.S.C § 112, second paragraph.

Claims 7-15, 21-30, 36-40 and 44-49 were rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it is allegedly unclear to what LMP-1s is referring.

A person with ordinary skill in the art at the time the instant invention was made would understand that LMP-1s is not just any shortened LMP-1s, but is a definite short version of human LMP-1. Specifically, LMP-1s refers to a truncated (short) version of HLMP-1, which resulted from a point mutation in one source of a cDNA clone, providing a stop codon which truncated the protein. *See e.g.,* U.S. Patent 6,300,127, Col. 3, lines 17-22. LMP-1s consists of 223 amino acid and is presented in U.S. Patent 6,300,127 as SEQ ID NO: 34. *See* U.S. Patent 6,300,127, Example 23.

Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

3. Rejections under 35 U.S.C § 103

In their response to the previous office action, Applicants argued that claims 7, 21, and 36 and all claims dependent on these claims are patentable over Hair et al. (U.S. Patent 6,521,750) or (U.S. 6, 858,431) in view of Nagahara et al. as well as over Boden (Endocrinology 1998, 139(12): 5125-5134) in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998. vol. 6, pages 306-317.). The Examiner found Applicants' arguments persuasive and withdrew the rejections.

The Examiner now rejects the instant claims as obvious in view of the references cited above in further view of Liu (Bone Miner. Res. 17(3): 406-414 (2002)). The Examiner argues that Liu discloses a truncated version of hLMP-1, LMP-1(t), which has less than 100% sequence homology with LMP-1, RLMP or LMP-1s. However, as explained above in regard to rejection under 35 U.S.C § 112, second paragraph, LMP-1s in Hair and the instant claims refers to the same protein as LMP-1(t) in Liu, or, in other words, LMP-1(t) has 100% homology with LMP-1s. Accordingly, LMP-1(t) is already disclosed in Hair and the Examiner has recognized that Hair et al. does not teach the claimed methods.

For at least these reasons, Applicants respectfully assert that the instant claims traverse the Examiner's rejection.

4. Double Patenting Rejections.

Claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6858431 ("the '431 patent") in view of Nagahara et al., and further in view of Liu et al. Claims 7-9 and 36-38 were also

rejected for the same reason over claims 1-13 of U.S. Patent 6,521,750 ("the '750 patent") in view of Nagahara et al., and further in view of Liu et al.

Similarly to the rejection under 35 U.S.C § 103, the Examiner withdrew the previous rejection based on double patenting over the '431 patent or the '750 patent in view of Nagahara et al., but made a new rejection over these references in further view of Liu et al. However, as set forth above, Liu et al.'s LMP-1(t) is the same protein as LMP-1s in the '431 patent, the '750 patent and the instant claims. Accordingly, the '431 patent or the '750 patent, Nagahara et al. and Liu et al. in combination do not render the present claims obvious.

In light of the foregoing, Applicants respectfully assert that the present claims, as amended, traverse the Examiners rejection, and Applicants respectfully request that the Examiner withdraw her nonstatutory obviousness-type double patenting rejection and allow these amended claims.

Additionally, claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 7,504,374 ("the '374 patent"). Applicants respectfully request that this rejection be held in abeyance until allowable subject matter is indicated.

5. Rejections under 35 U.S.C § 112

The rejection of claims 7-15, 21-30 and 36-40 under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement was maintained.

First, the Examiner argues that Applicants' arguments are not persuasive because the claims have not been limited to SEQ ID NO: 5. Applicants, however, believe that there is no need to limit the claims to SEQ ID NO: 5 because the current disclosure supports the genus of osteoinductive peptides that is broader than just SEQ ID NO: 5.

Claims 7, 21, and 36 recite that the osteoinductive peptide comprises at least one isolated osteoinductive region of an LMP-1. As Applicants explained in their communication filed on April 22, 2009, the amino acid sequences for LMP-1, LMP-2, and LMP-3, as well as for rat RLMP and LMP-1s have been disclosed in the prior art. See e.g., U.S. Patent Application Serial Nos. 10/292,951 and 10/382,844. Accordingly, a person having ordinary skill in the art can easily identify the amino acid sequence with the osteoinductive potential by comparing the

amino acid sequences of LMP-1, LMP-2, and LMP-3. Such sequence of 40 amino acids is presented in the instant specification as SEQ ID NO: 5.

However, the instant specification does not stop there, but also discloses a number of osteoinductive polypeptides comprising overlapping segments of SEQ ID NO: 5 that have demonstrated osteoiductive functionality. These peptides are represented by SEQ. ID. NOs 1-4 and 6-8. As shown in Fig. 6, introducing these peptides into cells as part of the fusion protein induces bone growth. However, as Fig. 6 shows, peptides represented by SEQ. ID. NOs 1-8 have varying degree of osteoinductive activity. For example, introducing into a cell 25 nM of Peptide of SEQ ID NO: 3 results merely in some bone growth, whereas lesser amount of Peptides of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 7 cause higher level of bone growth. Furthermore, although peptides SEQ ID NOs 1, 5, 6, and 8 resulted in similar degree of bone growth as the peptide of SEQ ID. NO 3, much smaller amounts of these peptides were used. Comparing the structure of Peptide of SEQ ID NO: 3 with the structure of other peptides reveals that the same amino acid sequence is present in all peptides, except Peptide of SEQ ID NO: 3. A person having ordinary skill in the art would have been able to identify this sequence as Gly Ala Pro Pro Pro Ala Asp Ser Ala (GAPPPADSA), and recognize its functional relationship to the osteoinductive activity.

Applicants respectfully refer the Examiner to the analysis of claim 1 in Example 9 of the Written Description Training Materials ("Materials"). Claim 1 of Example 9 was drawn to an isolated protein "comprising the amino acid sequence shown in SEQ ID NO: 3." The analysis of that claim notes that even though only a partial structure of a protein is disclosed, one of skill in the art would "recognize that the applicant was in possession of a structural feature shared by all members of the genus." The analysis further goes on to conclude that those of skill in the art would recognize that the applicant would have been in possession of the claimed genus at the time of filing, even though no members of the genus have been described by complete structure.

In this case, the factual scenario is highly similar and the evidence that the written description is satisfied is even stronger, at least because 8 members of the genus of osteoinductive peptides comprising at least one isolated osteoinductive region of an LMP-1 are disclosed in the instant specification. Accordingly, one having ordinary skill in the art would recognize that Applicants were in possession of the claimed genus as Applicants have disclosed a sufficient number of

species of the osteoinductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 genus in combination with description of the structure of the species that is responsible for the osteoinductive functionality of these species.

Second, the Examiner argues that one with ordinary skill would not have understood from the instant disclosure that administering of the claimed peptides to a cell would induce proteoglycan synthesis and osteoblast differentiation or have osteoinductive potential since the specification does not provide adequate description of the structural and functional relationship of the region that comprises such activity. Applicants respectfully disagree.

As explained above, the instant specification does teach that the presence of the sequence GAPPPADSA is responsible for the osteoinductive functionality of the claimed genus. Fig. 6 provides clear evidence that Peptides of SEQ ID NOs: 1-2 and 4-8, which include the sequence GAPPPADSA, are more effective in inducing bone growth than Peptide of SEQ ID NO: 3, which lacks the sequence GAPPPADSA. From this data, a person having ordinary skill in the art would have reasonably inferred that these peptides induce bone growth due, at least in part, to these peptides' ability to induce BMP synthesis because BMP's is known to play an important role in bone formation and growth. It is also well known that BMP increases proteoglycan production as well as induces osteoblast differentiation. *See e.g.*, U.S. Patent Application Serial Nos. 10/292,951. Therefore, the person of ordinary skill in the art would have concluded that the peptides that induce bone formation (e.g., peptides with osteoiductive functionality) would also induce proteoglycan synthesis and osteoblast differentiation and would have further concluded that this functionality is due to the presence of the sequence GAPPPADSA.

According to MPEP § 2163(II)(A)(3)(b), when a claim limitation is not explicitly described in the specification, the written description may be met by showing that such limitation is supported in the original disclosure implicitly or inherently. Applicants respectfully submit that a person with ordinary skill in the art would have understood from the instant disclosure that administering of the claimed peptides to a cell would induce proteoglycan synthesis and osteoblast differentiation.

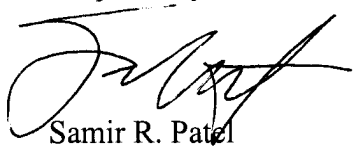
In light of the foregoing, Applicants respectfully request that the Examiner withdraw this ground for rejection.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns, and the claims of the instant application are in condition for allowance. Applicants request that any questions concerning this matter be directed to the undersigned at (901) 396-3133.

Please charge any deficiency and/or credit any overpayment to Deposit Account No. 132546. Thank you for your kind consideration in this matter.

Respectfully submitted,



Samir R. Patel
Registration No. 44,988

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Medtronic Spinal & Biologics
2600 Sofamor Danek Drive
Memphis, TN 38132
Telephone: 901-396-3133
Facsimile: 901-399-3040